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| APPLICATION NUMBER | FILING DATE | FIRST NAMED APPLICANT | ATTY. DOCKET NO. |
| 08/460,186 | 06/02/95 | VON BORSTEL | R 1331-138 |

EXAMINER

12M1/0527

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KUNZ, G

ART UNIT

PAPER NUMBER

1211

DATE MAILED: 05/27/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

- ☒ Responsive to communication(s) filed on 3-3-97
- ☒ This action is **FINAL**.
- ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire THREE month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

- ☒ Claim(s) 1-24 is/are pending in the application.
- Of the above, claim(s) _____ is/are withdrawn from consideration.
- ☐ Claim(s) _____ is/are allowed.
- ☒ Claim(s) 1-24 is/are rejected.
- ☐ Claim(s) _____ is/are objected to.
- ☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

- ☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- ☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
- ☐ The specification is objected to by the Examiner.
- ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- ☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
- ☐ received.
- ☐ received in Application No. (Series Code/Serial Number) _____.
- ☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

- ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- ☐ Notice of Reference Cited, PTO-892
- ☐ Information Disclosure Statement(s), PTO-1449, Paper No(s) _____
- ☐ Interview Summary, PTO-413
- ☐ Notice of Draftsperson's Patent Drawing Review, PTO-948
- ☐ Notice of Informal Patent Application, PTO-152

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-SEE OFFICE ACTION ON THE FOLLOWING PAGES-

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Applicant's amendment B filed 3-3-97 has been received and entered into the record.

Claims 1 - 25 are pending in the case.

All 35 USC statutes not cited in this case can be found cited in full in the first Office action mailed 9-3-96.

The obviousness-type double patenting rejection over Serial Nos. 08/472,210, 08/473,332, 08/186,485, and 08/465,455 is placed in abeyance as applicant requested until it is known which claims are deemed allowable.

Claims 1 - 15, 18 - 19, and 22 - 25 stand rejected under 35 USC 103 as being obvious over Martin et al. or Sommadossi et al. when taken in view of Von Borstel et al. (WO 89/03837) and Falcone et al. for the reasons already of record on pages 3 - 5 of the Office action mailed 9-3-96.

The applicant argues against this obviousness rejection on the grounds Von Borstel et al. describes the use of acylated uridine and cytidine for the treatment of many diseases but not for reducing the toxicity of chemotherapeutic agents. While this is true, it only means that Von Borstel et al. does not anticipate the instant claims. It does not establish that the combination of references cannot be combined for a prima facie case of obviousness. The person of ordinary skill in the art would clearly understand that Von Borstel et al. teaches the use of acylated uridine or cytidine for any condition known to respond favorably to free uridine. Martin et al. teaches that the toxicity of 5-FU is responsive to exogenous uridine. Therefore, the substitution of acylated uridine or cytidine for the free nucleoside is well within the ability of the artisan wanting

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to achieve higher sustained levels of uridine or cytidine in the blood without the drawbacks of diarrhea caused by administration of free uridine. The Falcone reference simply teaches the use of inhibitors of uridine phosphorylase as another way to increase blood and tissues levels of free uridine. Therefore, it would have also been obvious to have combined acylated uridine with an inhibitor of uridine phosphorylase in order to obtain the higher combined levels of blood and tissue uridine levels.

Secondly, the applicant argues that the use of acylated uridine or cytidine gives unexpectedly superior anticancer results when used with 5-fluorouracil (page 5, last two paragraph of amendment). 5-FU alone gave only partial regression in 50% of cases whereas in combination in with acylated uridine it gave 60 - 80% complete regression of established tumors. Furthermore, acylated uridine in combination with 5-FU showed a remarkable reduction in the gastrointestinal damage.

These unexpected results have been fully considered but are not deemed persuasive. These results might well be sufficient to overcome this obviousness rejection if they were submitted as part of an affidavit.

Claims 16 - 17 and 20 - 21 stand rejected under 35 USC 103 as being obvious over Bhalla et al. in view of Von Borstel et al. and Hanze for the reasons already of record on pages 5 - 6 of the first Office action mailed 9-3-96. The applicant argues that none of the references discloses the entire invention and that the combination of references does not render the invention obvious. This argument has been fully considered but is not deemed persuasive. A rejection under 35 USC

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103 means that no single reference discloses all of the critical elements of invention, otherwise the rejection would have been made under 35 USC 102. The combination of the references is clearly set forth in the first Office action. The substitution of acylated cytidine for cytidine in order to increase the blood and tissue levels of free uridine as taught by Von Borstel et al. in the method of Bhalla et al. would have obvious to the person of ordinary skill in the art at the time of the invention for the purpose of reducing the toxicity of cytidine analogs. In addition, the use of an inhibitor of cytidine deaminase as taught by Henze in combination with acylated cytidine would have been obvious to the artisan wanting the combined higher levels of free cytidine achieved by combining two different art recognized ways to increase serum cytidine.

Claims 1 - 3 - 15, 18 - 19, and 24 - 25 stand rejected under 35 USC 112, first paragraph, because the specification is only enabling for methods using the following specific non-methylated pyrimidine nucleosides: uridine, cytidine, 2'-deoxyuridine, and 2'-deoxycytidine. As written the instant claims embrace hundreds of different non-methylated pyrimidine nucleosides which would most likely increase toxicity rather than reduce the toxicity of chemotherapeutic agents. Such non-methylated pyrimidine nucleosides would include N4-propylcytidine, N4-cyclopropylcytidine, N4-cyclohexylcytidine, and thousands of additional nucleoside analogs.

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for response to this final action is set to expire **THREE MONTHS** from the date of this action. In the event a first response is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Kunz, whose telephone number is (703) 308-4623. The examiner can normally be reached on Tuesday through Friday from 6:30 AM to 4:00 PM. The examiner can also be reached on alternate Mondays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Kight, can be reached on (703) 308-0204. The fax phone number for this Group is (703) 308-4556. The fax phone number for this Group is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

Gary L. Kunz, Ph.D.
May 22, 1997


GARY L. KUNZ
PRIMARY EXAMINER
GROUP 1200